

University of Groningen

Two Cycles with One Catch

Wang, Yuanze; Patil, Pravin; Kurpiewska, Katarzyna; Kalinowska-Tluscik, Justyna; Domling, Alexander

Published in:
Acs combinatorial science

DOI:
[10.1021/acscombsci.7b00009](https://doi.org/10.1021/acscombsci.7b00009)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wang, Y., Patil, P., Kurpiewska, K., Kalinowska-Tluscik, J., & Domling, A. (2017). Two Cycles with One Catch: Hydrazine in Ugi 4-CR and Its Postcyclizations. *Acs combinatorial science*, 19(3), 193-198. <https://doi.org/10.1021/acscombsci.7b00009>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

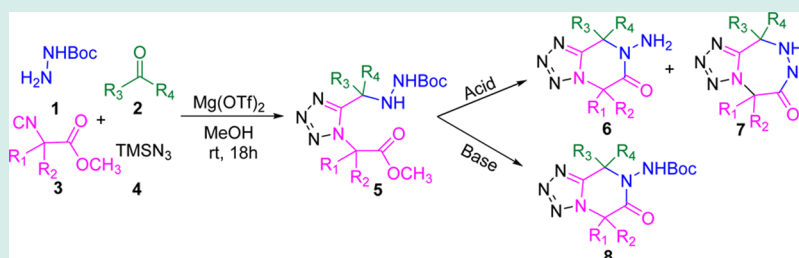
Two Cycles with One Catch: Hydrazine in Ugi 4-CR and Its Postcyclizations

Yuanze Wang,[†] Pravin Patil,^{†,‡} Katarzyna Kurpiewska,[‡] Justyna Kalinowska-Tluscik,[‡] and Alexander Dömling^{*,†,‡}

[†]University of Groningen, Department of Drug Design, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands

[‡]Jagiellonian University, Faculty of Chemistry, Department of Crystal Chemistry and Crystal Physics, Biocrystallography Group, Ingardena 3, 30-060 Krakow, Poland

S Supporting Information



ABSTRACT: Isocyanide-based multicomponent reactions (IMCR) are by far the most versatile reactions that can construct relatively complex molecules by one-pot synthesis. More importantly, the development of post IMCR modifications significantly improves the scaffold's diversity. Here, we describe the use of *N*-Boc protected hydrazine together with α -amino acid derived isocyanides in the Ugi tetrazole reaction and its post cyclization under both acidic and basic conditions. The cyclization in acidic conditions was conducted in a one pot fashion, which give 7-aminotetrazolopyrazinone (6) and tetrazolotriazepinone (7) cyclic products. The post cyclization under basic condition could selectively afford Boc-protected 7-aminotetrazolopyrazinone (8) products in yield of 38–87%.

KEYWORDS: isocyanide-based multicomponent reactions, hydrazine, post cyclization, tetrazole, one-pot synthesis, scaffolds diversity, European Lead Factory

INTRODUCTION

Small molecules have always been of great interest in medicinal chemistry and chemical genetics. They can provide oral leads for drug discovery while maintaining favorable cost-of-goods or can function as probes to illuminate the mechanism of the biological processes in the living systems.^{1–4} Such small molecule modulators are most commonly identified by high throughput screening of large compound collections. The European Lead Factory (ELF) supported by the Innovative Medicines Initiative (IMI) is aiming to bring together 500 000 high-quality compounds library from both academia and industry as the starting point for innovative drug discovery.⁵ A general consensus has emerged that library diversity, instead of library size, is a crucial consideration. Multicomponent reaction (MCR) chemistry is playing an important part in generating highly diverse compound libraries as it is capable of assembling novel molecular scaffolds and generating complex functionalization motifs in just a few steps on a short time scale.^{6–8} Furthermore, the exploitation of MCR-product postcyclization has also become a very popular strategy to generate complex skeletons.^{9–13}

Ugi/de-Boc/cyclize (UDC) chemistry has been successfully used in Hulme group.¹⁴ Recently, the application of the mono-

Boc protected hydrazine in the Ugi-tetrazole synthesis has been first explored in our lab.¹⁵ Herein, we show how α -amino acid derived isocyanides together with hydrazine can be used to obtain bicyclic scaffolds. We envisioned that both 6-membered (6) and 7-membered (7) products could be formed under the acidic conditions. Optimization of the protocol, with a particular emphasis to selective obtainment of 6-membered rings, as well as an application of the resulting compounds for further diversification, are described.

RESULTS AND DISCUSSION

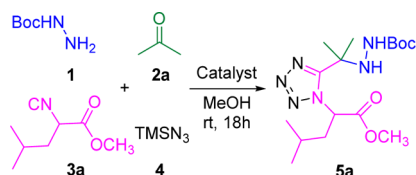
The reaction of Boc-hydrazine 1 with acetone 2a, isocyanide 3a, and trimethylsilyl azide 4 was performed in methanol at ambient temperature for 18 h which afforded a moderate yield of 5a (45%) (Scheme 1). It is well-known that Lewis acids could help the activation of the Schiff base and its formation which can be the rate-limiting step in the Ugi-4CR.¹⁶ Hence, we initiated our work by screening various Lewis acids such as CF₃SO₃Li, CF₃SO₃Ag, CF₃SO₃K, (CF₃SO₃)₂Mg,

Received: January 11, 2017

Revised: February 7, 2017

Published: February 9, 2017

Scheme 1. Synthesis of Ugi-Adduct (5a)



(CF₃SO₃)₂Zn, ZnCl₂, SnCl₂, (CF₃SO₃)₃In, and (CF₃SO₃)₃Al as the catalyst in the Ugi-4CR reaction (Table 1).

Table 1. Screening of the Lewis Acid Catalysts for Ugi-Tetrazole Adduct

entry	catalyst	conc. (equiv)	yield (%) ^a
1	-	-	45
2	ZnCl ₂	0.1	72
3	SnCl ₂	0.1	60
4	(CF ₃ SO ₃) ₂ Zn	0.1	62
5	CF ₃ SO ₃ Ag	0.1	43
6	CF ₃ SO ₃ K	0.1	47
7	(CF ₃ SO ₃) ₂ Mg	0.1	75
8	CF ₃ SO ₃ Li	0.1	53
9	(CF ₃ SO ₃) ₃ In	0.1	38
10	(CF ₃ SO ₃) ₃ Al	0.1	47

^aIsolated yield.

We found that divalent Lewis acid catalysts afforded high yields, (CF₃SO₃)₂Mg was found to be the best catalysts affording 75% yield of 5a. ZnCl₂ gave a similar good yield of 72%. In addition, (CF₃SO₃)₂Zn and SnCl₂ resulted in slightly lower yields (62% and 60%). In contrast, poorer yields were observed in the reactions catalyzed by other commonly used Lewis acids. Hence, (CF₃SO₃)₂Mg was the Lewis acid catalyst of choice for the subsequent explorations.

With the optimal catalyst for Ugi-4CR in hand, the conditions for postcyclization were further optimized. At first, we tried to cyclize the Ugi-adduct under acidic conditions in one pot (Scheme 2). We speculated that it is possible to form both 6-membered (6) and 7-membered (7) cyclized products as the Boc-protecting group will be removed in acidic condition. Although the 7-membered product suffered from more strain during the ring formation than the 6-membered product, the exposed primary amine would be also highly interesting for further transformations.

We commenced our one pot postcyclization under acidic conditions using Ugi-adduct 5a. Four different acids: trifluoroacetic acid, acetyl chloride, 6 M aqueous hydrochloric acid, and 2 M methanolic hydrochloric acid were screened (Table 2). Results showed that two equivalents of trifluoroacetic acid afforded poor yields of 6a (10%) and traces of 7a. When 6 M aqueous hydrochloric acid solutions was used as the solvent, a 33% yield of the 6-membered product (6a) was afforded.

Table 2. Screening of Acidic Conditions for Post-cyclization

entry	acid, solvent	amount, time	yield (%) ^a	
			6a	7a
1	TFA, MeOH	2 equiv., 18 h	10	traces
2	6 M aq. HCl	5 mL, 18 h	33	traces
3	acetyl chloride, MeOH	2 equiv., 18 h	36	5
4	2 M HCl in MeOH	5 mL, 4 h	64	6

^aIsolated yield.

Interestingly, two equivalent of acetyl chloride in methanol as solvent gave 36% yield of the 6-membered product (6a), as well as little amount of 7-membered product (7a, 5% yield). Surprisingly, when we used 2 M methanolic hydrochloric acid as solvent, the yield of 6-membered (6a) product significantly increased to 64% and minor 7-membered (7a) product (6% yield) was formed. Hence, 2 M methanolic hydrochloric acid was chosen as the acid for postcyclization. Furthermore, we explored the possibility to accomplish the overall 2-step sequence in a one-pot fashion. The unpurified Ugi-adduct obtained was directly treated with 2 M methanolic hydrochloric acid. We were pleased to observe that 43% of yield 6-membered product 6a and 6% yield of 7-membered product 7a could be obtained in the one-pot procedure. After these interesting results, the generality of this one-pot procedure was then explored by varying the isocyanide and oxo-components (Table 3).

Various derivatives of methyl glycine isocyanides along with ketones and aldehydes were synthesized. When we used methyl glycine isocyanides with acetone, 6-membered ring 6b was obtained in 33% yield. Surprisingly, with cyclohexanone we observed only a minor amount of 6-membered ring 6c (7% yield) along with spiro-7-membered ring 7c (34% yield). A similar trend was observed with isovaleraldehyde, that gave 7-membered ring 7d in 29% yield accompanied by 6d in only trace amount. With hydrocinnamaldehyde (entry 5), we obtained 6e in 27% yield along with 10% yield of 7-membered ring (7e). Similar results were obtained with isobutyraldehyde (entry 6), in this case we obtained 24% yield of 6f and 10% yield of 7f. In addition, the isocyanide derived from methyl phenylalaninate was used in combination with various oxo components. With cyclopropanecarboxaldehyde (entry 7) and acetone (entry 8) we obtained only 6-membered ring 6g and 6h in 23% and 30% yield, respectively. Cyclopentanone (entry 10), hydrocinnamaldehyde (entry 11) and isobutyraldehyde (entry 12) gave only 6-membered ring 6j (34% yield), 6k (15% yield) and 6l (35% yield). In case of 6k and 6l, we observed the diastereomeric mixtures in 25:1 and 1:1 ratio, respectively. Cyclohexanone gave 6i (16% yield) and 7i (26% yield). Interestingly, in the final 7-membered product 7i we observed a mixture of two ring-flip conformers in 1:1 ratio in the NMR spectra. A similar phenomenon is often observed in the related 7-membered benzodiazepines based on ring flipping and axial

Scheme 2. One-Pot Cyclization of Ugi-Adduct under Acidic Condition

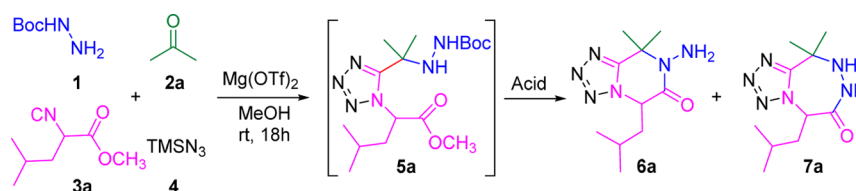
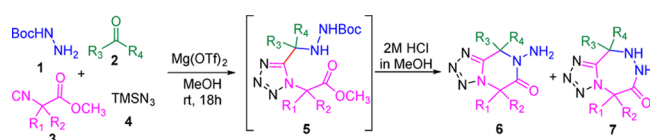


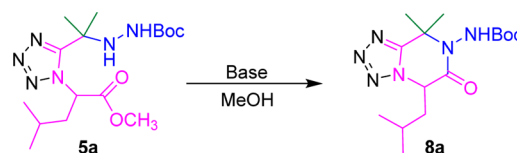
Table 3. Typical Structures and Yields of Post-Cyclization Product under Acid Condition


entry	R_1 R_2 (3)	R_3 R_4 (2)	6	7
1			6a , 64	7a , 6
2			6b , 33	-
3			6c , 7	7c , 34
4			-	7d , 29
5			6e , 27	7e , 10
6			6f , 24	7f , 10
7			6g , 23	-
8			6h , 30	-
9			6i , 16	7i , 26
10			6j , 34	-
11			6k , 15 ^b	-
12			6l , 35 ^c	-
13			6m , 38	-
14			-	7n , 40
15			6o , 38	7o , 6

^aOne-pot isolated yields. ^bdr ratio = 25:1. ^cdr ratio = 1:1.

and equatorial orientation of bulky substituents. Furthermore, we tested the isocyanide derived from valine methyl ester with various oxo-components like acetone and cyclohexanone. Surprisingly, we were able to isolate only the 6-membered ring **6m** in 38% yield with acetone and exclusively the 7-membered ring **7n** in 40% yield with cyclohexanone. With cyclopentanone (entry 15) we obtained 6-membered and 7-membered ring **6o** and **7o** in 38% and 6% yield, respectively. Although the overall yield of the one-pot reaction under acidic condition is relatively low, we were surprised to find that both 6-membered and 7-membered products were obtained. As we can see from cyclization products **6e** and **7e**, **6f** and **7f**, and **6o** and **7o**, 6-membered product was formed as the major product and the 7-membered product was formed in less than 10%

yield. Notably, when cyclohexanone was used as the oxo-component, the 7-membered ring was observed as the major product (**7c**, **7i**, and **7n**). In general the yields and selectivity of the reaction under acidic conditions was unsatisfactory. Therefore, we tried to cyclize the Ugi-adduct under basic conditions (Scheme 3, Table 4).

Scheme 3. Cyclization under Basic Conditions**Table 4. Screening of Basic Conditions for Post-cyclization**

entry	catalyst	conc. (equiv)	time (h)	yield (%) ^a
1	DIPEA	0.1	1	20
2	DIPEA	0.1	12	25
3	NaOCH ₃	0.1	1	33
4	NaOCH ₃	0.1	12	40
5	NaOCH ₃	1	1	86
6	NaOCH ₃	2	1	80

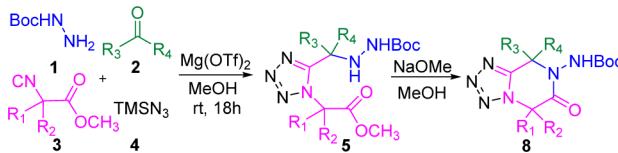
^aIsolated yield.

As the Boc-protecting group is generally stable under basic conditions, only the 6-membered products with the Boc-group on are expected to be formed. Initially, two bases (DIPEA and NaOCH₃) which are often used in cyclization chemistry were evaluated. It was found that when they were used in catalytic amounts, very poor yield was observed in both cases after 1h. In addition, prolonging the reaction time from 1 to 12 h had little effect either. As NaOCH₃ has given higher yield than DIPEA, we further increased the amount of NaOCH₃ to one equivalent, which significantly improved the reaction yield to 86%. However, increasing the base amount to two equivalents failed to further improve the reaction yield.

The results of the cyclization under basic condition are summarized in Table 5. We tested different methyl glycine isocyanide derivatives obtained from various amino acids in Ugi-tetrazole reaction with the various oxo-components. To avoid the formations of diastereomeric mixture after the post modification on Ugi-adducts, we selected symmetric ketones as oxo-components. Interestingly, with magnesium triflate as Lewis acid catalyst in the Ugi-tetrazole reaction, good to excellent yields of adducts (**5a–5l**, 56–90%) was obtained. These pure isolated Ugi-tetrazole adducts were subjected to cyclization with sodium methoxide (1 equiv) in methanol (0.5 M) at room temperature. All Ugi-tetrazole adducts (**5a–5l**) gave 6-membered cyclized product (**8a–8l**) in moderate to excellent yields (38–87%). Furthermore, we wanted to develop this reaction sequence in one pot. To test this strategy, we selected the methyl leucine isocyanide with acetone as an oxo-component, mono-Boc hydrazine and TMSN₃. We observed the Ugi tetrazole adduct formation was good by SFC-MS and TLC analysis. After the addition of sodium methoxide in the reaction mixture for basic cyclization, we observed multiple product formation. The major side product was the hydrolyzed methyl ester of the Ugi-tetrazole adducts to the corresponding acids; however, **8a** was isolated only in 41% yield.

As we observed the one pot postcyclization under acidic condition using Ugi-adduct **5** was poor yielding to compounds

Table 5. Typical Structures and Yields of Post-cyclization Product under Basic Condition



entry	R_1 R_2	R_3 R_4	5	8
1	CH_3 CH_2COOMe	CH_3 CH_3	5a, 73	8a, 83
2	CH_3 CH_2COOMe	CH_2 CH_2	5b, 90	8b, 78 (4:6) ^a
3	CH_3 CH_2COOMe	CH_2 CH_2	5c, 58	8c, 77 (4:6) ^a
4	CN COOMe	CH_2 CH_2	5d, 76	8d, 38
5	C_6H_5 CH_2COOMe	CH_3 CH_3	5e, 63	8e, 83
6	C_6H_5 CH_2COOMe	CH_2 CH_2	5f, 56	8f, 74
7	CH_3 COOMe	CH_3 CH_3	5g, 76	8g, 87
8	CH_3 COOMe	CH_2 CH_2	5h, 56	8h, 81 (3:7) ^a
9	CH_3 COOMe	CH_2 CH_2	5i, 73	8i, 87 (3:7) ^a
10	CH_3 COOMe	C_6H_4 N	5j, 81	8j, 79 (4:6) ^a
11	CH_3 COOMe	CH_2 CH_2	5k, 57	8k, 80
12	C_6H_4 CH_2COOMe	CH_3 CH_3	5l, 82	8l, 69 (1:1) ^b

^aIsolated yields. ^bN-Boc rotamers.

6. We further deprotected the compounds 8 under acidic condition using 2 M methanolic hydrochloric acid at room temperature for 18h (Table 6). We obtained exo-NHBoc deprotected compounds as hydrochloric salts (9) in excellent yields after evaporation of solvents.

To further support structural proof, we were also able to grow crystals of some Ugi-adducts, 6-membered products and 7-membered products (Figure 1).

Lastly, the diversity application of the free exo-NH₂ group in compounds 6a for biological studies was accomplished by synthesizing some derivatives through acylation, sulfonylation and thiourea formation (Scheme 4). Compounds 6a reacted with 1.2 equiv of acryloyl chloride to give compound 10 in 78% yields. Upon treatment with 4-chlorobenzoyl chloride in DCE under reflux, compound 11 (75% yield) was afforded. The reaction of 6a with 4-methylbenzenesulfonyl chloride led to 12

Table 6. Deprotection of Compound 8

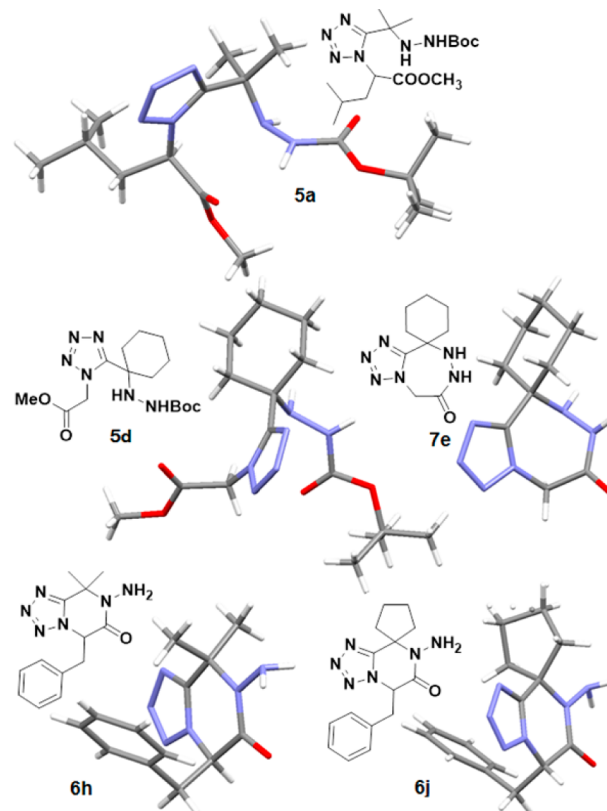
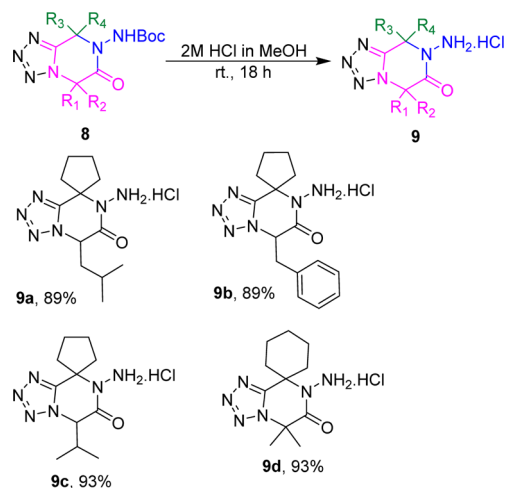


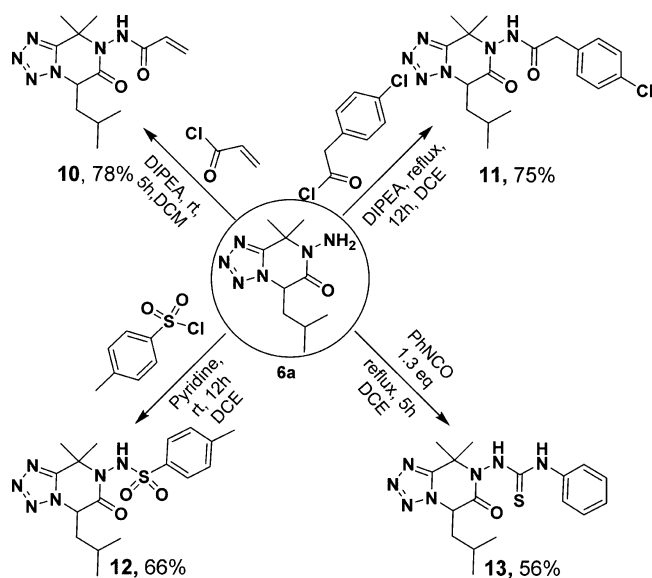
Figure 1. Crystal structures of 5a, 5d, 7e, 6h and 6j.

in 66% yield. In addition, 6a was also subjected to phenyl thioisocyanate with pyridine in DCE to give 13 in 56% yield.

CONCLUSIONS

In summary, we described here the application of mono-Boc-protected hydrazine in the Ugi tetrazole synthesis and its postcyclization. Both 7-aminotetrazolopyrazinone (6) and tetrazolotriazepinone (7) products were afforded in one-pot under acidic conditions. Under basic condition, Boc-protected 7-aminotetrazolopyrazinone (8) products were obtained in good to excellent yield. The exposed free primary amine could be further used as the building block to synthesize more complex compounds.

Scheme 4. Application of the Primary Amine in Ugi-Adduct 6a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.7b00009.

Experimental procedures, compound data, NMR spectra, HRMS, and crystal structure determinations (PDF)

Crystallographic information file for compound 5a (CIF)

Crystallographic information file for compound 5d (CIF)

Crystallographic information file for compound 6h (CIF)

Crystallographic information file for compound 6j (CIF)

Crystallographic information file for compound 7e (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: (+31)503637582. E-mail: a.s.s.domling@rug.nl. Website: www.drugdesign.nl.

ORCID

Pravin Patil: 0000-0002-0903-8174

Alexander Dömling: 0000-0002-9923-8873

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported (A.D.) by the NIH (2R01GM097082-05), the Innovative Medicines Initiative (Grant Agreement No. 115489), and received funding from the European Union's Horizon 2020 research and innovation program under MSC ITN "Accelerated Early stage drug discovery" (AEGIS), Grant Agreement No. 675555. K. K, K-T. J supported by the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (Contract No. POIG.02.01.00-12-023/08). We acknowledge the China Scholarship Council for supporting Y.W.

■ REFERENCES

- (1) Adams, J. L.; Smothers, J.; Srinivasan, R.; Hoos, A. Big opportunities for small molecules in immuno-oncology. *Nat. Rev. Drug Discovery* **2015**, *14*, 603–622.
- (2) Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. K.; Jimmidi, R.; Jogula, S.; Arya, P. Small molecule modulators of protein–protein interactions: selected case studies. *Chem. Rev.* **2014**, *114*, 4640–4694.
- (3) Doyle, S. K.; Pop, M. S.; Evans, H. L.; Koehler, A. N. Advances in discovering small molecules to probe protein function in a systems context. *Curr. Opin. Chem. Biol.* **2016**, *30*, 28–36.
- (4) Arkin, M. R.; Tang, Y.; Wells, J. A. Small-molecule inhibitors of protein-protein interactions: progressing toward the reality. *Chem. Biol.* **2014**, *21*, 1102–1114.
- (5) (a) Besnard, J.; Jones, P. S.; Hopkins, A. L.; Pannifer, A. D. The joint european compound library: Boosting precompetitive research. *Drug Discovery Today* **2015**, *20*, 181–186. (b) Hamza, D.; Kalliokoski, T.; Pouwer, K.; Morgentin, R.; Nelson, A.; Müller, G.; Piechot, D.; Tzalis, D.; et al. Expansion of chemical space for collaborative lead generation and drug discovery: the European Lead Factory Perspective. *Drug Discovery Today* **2015**, *20*, 1310–1316. (c) Mullard, A. European lead factory opens for business. *Nat. Rev. Drug Discovery* **2013**, *12*, 173–175. (d) Nelson, A.; Roche, D. Innovative approaches to the design and synthesis of small molecule libraries. *Bioorg. Med. Chem.* **2015**, *23*, 2613. (e) Paillard, G.; Cochrane, P.; Jones, P. S.; Caracoti, A.; van Vlijmen, H.; Pannifer, A. D. The ELF Honest Data Broker: informatics enabling public–private collaboration in a precompetitive arena. *Drug Discovery Today* **2016**, *21*, 97–102.
- (6) Domling, A. Recent developments in isocyanide based multi-component reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17–89.
- (7) Dömling, A.; Wang, W.; Wang, K. Chemistry and biology of multicomponent reactions. *Chem. Rev.* **2012**, *112*, 3083–3135.
- (8) Zhu, J.; Bienayme, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
- (9) Sinha, M. K.; Khoury, K.; Herdtweck, E.; Dömling, A. Various cyclization scaffolds by a truly Ugi 4-CR. *Org. Biomol. Chem.* **2013**, *11*, 4792–4796.
- (10) Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. A Universal Isocyanide for Diverse Heterocycle Syntheses. *Org. Lett.* **2014**, *16*, 5736–5739.
- (11) Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. MCR synthesis of a tetracyclic tetrazole scaffold. *Bioorg. Med. Chem.* **2015**, *23*, 2699–2715.
- (12) Zarganes-Tzitzikas, T.; Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. Concise Synthesis of Tetrazole–Ketopiperazines by Two Consecutive Ugi Reactions. *Eur. J. Org. Chem.* **2015**, *2015*, 51–55.
- (13) Erb, W.; Neuville, L.; Zhu, J. Ugi-post functionalization, from a single set of Ugi-adducts to two distinct heterocycles by microwave-assisted palladium-catalyzed cyclizations: tuning the reaction pathways by ligand switch. *J. Org. Chem.* **2009**, *74*, 3109–3115.
- (14) (a) Tempest, P.; Ma, L.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. Two-step solution-phase synthesis of novel benzimidazoles utilizing a UDC (Ugi/de-Boc/cyclize) strategy. *Tetrahedron Lett.* **2001**, *42*, 4959–4962. (b) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. Short solution phase preparation of fused azepine-tetrazoles via a UDC (Ugi/de-Boc/cyclize) strategy. *Tetrahedron Lett.* **2002**, *43*, 3681–3684. (c) Gunawan, S.; Ayaz, M.; De Moliner, F.; Frett, B.; Kaiser, C.; Patrick, N.; Xu, Z.; Hulme, C. Synthesis of tetrazolo-fused benzodiazepines and benzodiazepinones by a two-step protocol using an Ugi-azide reaction for initial diversity generation. *Tetrahedron* **2012**, *68*, S606–S611. (d) Xu, Z.; Ayaz, M.; Cappelli, A. A.; Hulme, C. General one-pot, two-step protocol accessing a range of novel polycyclic heterocycles with high skeletal diversity. *ACS Comb. Sci.* **2012**, *14*, 460–464.
- (15) Patil, P.; Zhang, J.; Kurpiewska, K.; Kalinowska-Thüscik, J.; Dömling, A. Hydrazine in the Ugi Tetrazole Reaction. *Synthesis* **2016**, *48*, 1122–1130.
- (16) (a) Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. A. Titanium catalysis in the Ugi reaction of α -amino acids

with aromatic aldehydes. *Org. Lett.* **2004**, 6, 3281–3284. (b) Dai, W. M.; Li, H. Lewis acid-catalyzed formation of Ugi four-component reaction product from Passerini three-component reaction system without an added amine. *Tetrahedron* **2007**, 63, 12866–12876. (c) Bongers, K. M.; Wennekes, T.; Filippov, D. V.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S. The Effect of Lewis Acids on the Stereochemistry in the Ugi Three-Component Reaction with D-lyxo-Pyrroline. *Eur. J. Org. Chem.* **2008**, 2008, 3678–3688. (d) Li, Z.; Sharma, U. K.; Liu, Z.; Sharma, N.; Harvey, J. N.; Van der Eycken, E. V. Diversity-Oriented Synthesis of β -Lactams and γ -Lactams by Post-Ugi Nucleophilic Cyclization: Lewis Acids as Regioselective Switch. *Eur. J. Org. Chem.* **2015**, 2015, 3957–3962.